Impact of neoadjuvant chemoradiotherapy followed by surgical resection on node-negative T3 and T4 non–small cell lung cancer

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Objective: This study examined the impact of neoadjuvant chemotherapy and concurrent high-dose radiation therapy on survival in patients with node-negative T3 and T4 non–small cell lung cancer.

Methods: A total of 110 consecutive patients underwent surgical resection for invasive T3N0M0 (94 patients) and T4N0M0 (16 patients) non–small cell lung cancer between 1979 and 2008. Forty-seven patients received neoadjuvant chemotherapy and concurrent high-dose (5940 cGy) radiation therapy before resection (Chemo-RT group). Sixty-three patients underwent surgical resection without receiving induction chemoradiotherapy (Surg group), of whom 21 received neoadjuvant radiation, 19 received adjuvant radiation, 17 received surgery alone, 2 received adjuvant chemotherapy, 2 received adjuvant chemoradiotherapy, and 2 received brachytherapy. Survival of the Chemo-RT and Surg groups was compared using both crude and adjusted Cox proportional hazards models.

Results: The 5-year, 10-year, and median survivals were 61%, 50%, and 90 months, respectively, in the Chemo-RT group versus 22%, 14%, and 22 months, respectively, in the Surg group. Subjects in the Surg group had an increased risk of death (hazard ratio, 2.60; 95% confidence interval, 1.62–4.18; $P = .0001$) compared with the Chemo-RT group. After adjustment for potential confounding variables of age, sex, tumor size, tumor location, type of operation, and decade of care, subjects in the Surg group remained at increased risk of death (hazard ratio, 2.81; 95% confidence interval, 1.45–5.44, $P = .002$) compared with the Chemo-RT group.

Conclusions: Aggressive treatment of node-negative invasive T3 and T4 NSCLC with induction chemoradiotherapy may significantly prolong survival. This approach should be evaluated in a prospective multicenter national trial. (J Thorac Cardiovasc Surg 2011;141:1392-7)

The lung cancer staging system outlines the T3 and T4 tumor descriptor as a diverse group of locally advanced tumors. In general, T3 tumors are resectable, and T4 tumors are generally unresectable because of their invasion into adjacent organs or major vessels. T3 and T4 tumors may be central or peripheral. Peripheral T3 tumors may involve the parietal pleura, chest wall, diaphragm, or superior sulcus. Central T3 tumors invade the mediastinal pleura or fat, or may involve the pericardium or central bronchus within 2 cm of the carina. Peripheral T4 tumors invade the vessels in the superior sulcus or the vertebral body, and central T4 tumors invade the left atrium, aorta, or intrapericardial portion of the main pulmonary arteries, or involve the esophagus or carina.

Unfortunately, many of these T3 and T4 lung cancers have associated lymph node involvement. When N2 disease is present, survival is poor and resection is generally contraindicated.[1,2] Likewise, incomplete resection has been associated with a dismal prognosis.[3] Our favorable results with induction-concurrent chemoradiotherapy in patients with N2 disease have led us to use this approach in many node-negative patients with T3 and T4 tumors to increase the likelihood of an R0 resection and treat unsuspected micro-metastatic nodal or systemic disease.[4]

This report presents our results in these patients with node-negative locally advanced tumors, comparing treatment outcomes in patients who received induction chemoradiotherapy (Chemo-RT) with those who did not (Surg).

MATERIALS AND METHODS

Since 1979, we have maintained a prospective database on all patients undergoing resection for lung cancer. Patient tracking is ongoing, and no patient has been lost to follow-up. Patients undergoing resection between August 1979 and April 2008 were evaluated, and those with predominantly bronchioalveolar cell lung cancers were excluded.

In 2009, the International Association for the Study of Lung Cancer upgraded T2 tumors greater than 7 cm in diameter to T3 and downgraded T4 tumors characterized by intralobar satellite nodules to T3.[5] These changes updated the Fifth Edition of the *American Joint Committee on Cancer (AJCC) Cancer Staging Manual* (1997).[6] We used the Fifth Edition in this report because our patients were prospectively staged. However,

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Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
FEV_1 = forced expiratory volume in 1 second
HR = hazard ratio
NSCLC = non–small cell lung cancer
PET = positron emission tomography

patients whose T status depended on the presence of satellite nodules were excluded because those tumors are generally not invasive (although they indicate a poorer prognosis). Patients with invasive tumors were treated as having stage III non–small cell lung cancer (NSCLC) according to the protocol at the time.

All patients had a complete history and physical, and a chest computed tomography (CT) scan. Since 2000, patients with suspected lung cancer have undergone a positron emission tomography (PET) scan. All patients had complete pulmonary function testing, and most of those aged more than 50 years had a cardiac stress test. Brain CT or magnetic resonance imaging was performed preoperatively to exclude brain metastases. In patients receiving induction therapy, the T status was determined by history and CT. Patients without direct evidence of chest wall invasion, who had tumor abutting the chest wall and pain localized to that area, were considered to have T3 tumors. In patients receiving no induction therapy, the T status was determined by pathology. All patients had staging of the mediastinal lymph nodes by CT and invasive staging when enlarged or PET-positive lymph nodes were identified in the mediastinum. However, routine invasive staging for all patients with T3 or T4 tumors was not carried out early in this series. Tumors located in the inner third of the lung field, as visualized on CT, and those visualized by bronchoscopy were considered to be central tumors. No distinction was made between peripheral lung cancers invading the chest wall and superior sulcus tumors. These tumors were classified according to their T descriptor. Tumor size was determined by pathology in patients who received no induction therapy and by CT in patients who received neoadjuvant therapy. All operations were performed by thoracotomy. Patients receiving concurrent high-dose radiation and chemotherapy were managed by a strict protocol postoperatively, as reported previously.[4] In patients with peripheral tumors, an extrapleural resection without chest wall resection was carried out if the pleura easily stripped from the chest wall. If there was any adherence, an en bloc chest wall resection was performed.

The 2 groups of patients (Chemo-RT vs Surg) were compared using clinical and demographic characteristics (Table 1). Continuous variables were compared using the Student *t* test or Wilcoxon rank-sum tests. Categoric variables were compared with Fisher's exact test; chi-square testing was used for analyses of variables with more than 2 categories. Comparisons of survival were made with Cox proportional hazards models. The proportional hazards assumption was met. To control for potential confounding variables of the association between neoadjuvant chemoradiotherapy and survival, an a priori model was used, with age, sex, forced expiratory volume in 1 second (FEV_1), tumor size, tumor location (central vs peripheral), operation type (total pneumonectomy vs lesser resection), and decade of care entered into the model with neoadjuvant chemoradiotherapy status. In addition, we performed a propensity score-adjusted regression analysis, with propensity scores for receipt of chemotherapy calculated from logistic regression models, including all measured covariates as predictors of chemotherapy status. Kaplan–Meier curves with log-rank testing demonstrated unadjusted differences in survival between the 2 treatment categories. All statistical analyses, with the exception of the generation of Kaplan–Meier survival curves (SPSS v 17; SPSS Inc, Chicago, IL), were carried out with SAS v 9.1 software (SAS Institute Inc, Cary, NC). This study was approved by the Boston University Internal Review Board.

RESULTS

A total of 110 patients (94 with T3 and 16 with T4 node-negative NSCLC) underwent resection. Forty-seven patients received induction chemoradiotherapy (Chemo-RT group) consisting of external beam radiotherapy (≥5940 cGy) and concurrent chemotherapy. Thirty-eight patients received a cisplatinum doublet, 8 patients received a carboplatinum doublet, and 1 patient with a kidney transplant received paclitaxel alone. Thirty-eight of these patients (77%) underwent mediastinoscopy before induction therapy.

Sixty-three patients underwent surgical resection without induction chemoradiotherapy (Surg group). Seventeen patients underwent surgery alone, 21 patients underwent induction radiotherapy, 19 patients underwent adjuvant radiotherapy, 2 patients underwent intraoperative brachytherapy, 2 patients underwent adjuvant chemotherapy, and 2 patients underwent adjuvant chemoradiotherapy (Table 2). Twenty-four of these patients underwent mediastinoscopy (38%), and 2 of these patients underwent Chamberlain procedures. The type of resection performed in both groups is shown in Table 2. A sublobar resection was performed only when pulmonary function or performance status was compromised.

The disease pattern responsible for each T descriptor assignment is shown in Table 3. When compared with the Surg group, a higher percentage of patients in the Chemo-RT group had chest wall or mediastinal fat invasion as opposed to parietal pleura involvement, which accounted for their T3 assignment.

Table 1 demonstrates the clinical and demographic characteristics of the study population. Subjects who received neoadjuvant chemotherapy had a higher FEV_1 (2.37 ± 0.78 L vs 2.00 ± 0.67 L, $P = .02$) and were more likely to have had more recent care (in the 1990s and 2000s, rather than the 1980s, $P = .001$).

In the unadjusted model, subjects who did not receive neoadjuvant chemotherapy had an increased risk of death (hazard ratio [HR], 2.60; 95% confidence interval [CI], 1.62–4.18; $P = .0001$) compared with subjects who had neoadjuvant chemotherapy. The 5-year, 10-year, and median survivals were 61%, 50%, and 90 months, respectively, in the Chemo-RT group versus 22%, 14%, and 22 months, respectively, in the Surg group.

After adjustment for a priori-defined potential confounding variables of age, FEV_1, T descriptor, tumor size, sex, central or peripheral location of tumor, operation type, and decade of care, subjects in the Surg group alone remained at increased risk of death (HR, 2.81; 95% CI, 1.45–5.44; $P = .002$; Figure 1, *A*) compared with subjects who had neoadjuvant chemotherapy. Results were similar

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TABLE 1. Clinical and demographic subject characteristics

Variable mean (SD) or N (%)	Total N = 110, unless otherwise specified	Chemo-RT N = 47	Surg N = 63	*P*
Age, y	62.3 ± 9.7	60.5 ± 10.4	63.7 ± 9.0	.09
Sex = male	75 (68%)	26 (55.3%)	46 (73.0%)	.07
T descriptor = 3	91 (82.7%)	36 (76.6%)	55 (83.7%)	.20
Tumor size, cm; N = 108	5.31 ± 2.6	5.54 ± 2.4	5.16 ± 2.7	.27
Central tumor	42 (38.2%)	22 (46.8%)	20 (31.8%)	.12
FEV_1, L	2.15 ± 0.74	2.37 ± 0.78	2.0 ± 0.67	.02†
Pneumonectomy‡	22 (20%)	12 (26%)	10 (17%)	.24
Complete pathologic response; N = 71	30 (43.5%)	21 (45.7%)	9 (39.1%)*	.80
Cell type:				.78
Squamous	42 (38.2%)	17 (36.2%)	25 (39.7%)	
Adenocarcinoma	32 (29.1%)	13 (27.7%)	19 (30.2%)	
Adenosquamous	8 (7.3%)	4 (8.5%)	4 (6.3%)	
Non–small cell (NOS)	28 (25.5%)	13 (27.7%)	15 (23.8%)	
Decade of care				.001†
1980s	45 (40.9%)	1 (2.13%)	44 (69.8%)	
1990s	36 (32.7%)	23 (48.9%)	13 (20.6%)	
2000s	29 (26.4%)	23 (48.9%)	6 (5.5%)	

FEV_1, Forced expiratory volume in 1 second; *NOS,* not otherwise specified; *SD,* standard deviation. *Twenty-one patients received induction external radiation therapy. †Statistically significant *P* value. ‡Remaining patients underwent the operations listed in Table 2.

TABLE 3. Factor responsible for the T descriptor

	T3 tumors	
	Chemo-RT group	**Surg group**
Parietal pleura	N = 8; 21%	N = 30; 53%
Chest wall	N = 16; 42%	N = 19 34%
Mediastinal fat	N = 10; 26%	N = 4; 7%
Diaphragm	N = 1; 3%	N = 1; 2%
<2 cm carina	N = 3; 8%	N = 2; 4%
Total	N = 38; 100%	N = 56; 100%
	T4 tumors	
	Chemo-RT group	**Surg group**
PA/atrium	N = 7; 78%	N = 7; 100%
Vertebral body	N = 1; 11%	N = 0; 0%
Subclavian artery	N = 1; 11%	N = 0; 0%
Total	N = 9; 100%	N = 7; 100%

PA, Pulmonary artery.

for the propensity score-adjusted model (HR 2.69; 95% CI, 1.33–4.4; $P = .006$).

In addition to the absence of neoadjuvant chemoradiotherapy, significant univariate predictors of mortality were age (HR per year, 1.058; 95% CI, 1.03–1.08; $P = .0001$), FEV_1 (HR per liter, 0.552; 95% CI, 0.41–0.75; $P = .0001$), and decade of care (HR 0.70 with each increased decade of care; 95% CI, 0.52–0.93; $P = .015$). Including these variables in 1 model demonstrated that the only independent predictors of increased mortality were older patients (HR, 1.06; 95% CI, 1.03–1.09; $P = .0004$) and absence of neoadjuvant chemotherapy (HR, 2.34; 95% CI, 1.27–4.31; $P = .007$). In the Chemo-RT group, the tumor location, type of resection, presence or absence of residual tumor (data not available for 1 patient), and T status did not affect survival.

TABLE 2. Type of resection

Type	Chemo-RT N	Chemo-RT %	Surg N	Surg %
Pneumonectomy	12	25%	10	16%
Bilobectomy	4	9%	3	5%
Lobectomy	26	55%	43	68%
Segmental resection	1	2%	1	2%
Wedge resection	4	9%	6	9%
Total	**47**	**100%**	**63**	**100%**

Median survival was greatest for those who received surgical resection and neoadjuvant chemoradiotherapy (90 months; 95% CI, 46; no estimate is available), compared with resection and adjuvant external radiation therapy (25 months; 95% CI, 12–67), resection and neoadjuvant external radiation therapy (19 months; 95% CI, 8–37), or resection alone (19 months; 95% CI, 7–27; $P = .0001$; Figure 1, *B*).

In the Surg group, 5 of the 63 resected patients had positive margins. All had T3 tumors: 3 at a lung margin and 2 in the chest wall. Three of these 5 patients received postoperative radiation therapy and subsequently died of lung cancer at 12, 19, and 28 months. One of these was an operative death; also, 1 patient died of cardiovascular disease at 64 months. In the Chemo-RT group, 4 of the 47 patients undergoing resection had positive margins: 2 at the lung margin and 2 in the peribronchial lymphatics. In 1 patient, the mediastinal tissue also was positive for tumor. All 4 patients received postoperative chemotherapy. The 2 patients with tumor at the lung margin died of lung cancer at 10 and 22 months. The other 2 patients are alive at 91 and 94 months.

Of the 30 patients in the Surg group who had involvement of the parietal pleura without chest wall involvement, 3 underwent a chest wall resection, 1 of whom had a chest wall recurrence. Only 1 of the patients who did not have a chest wall resection had a chest wall recurrence. In the

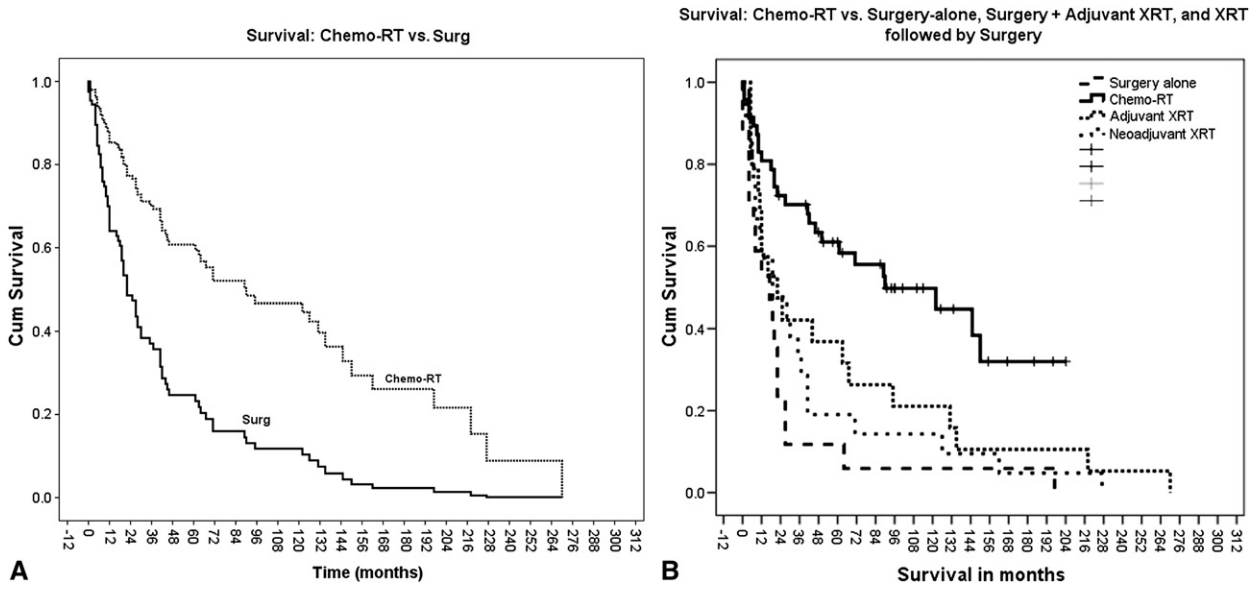

FIGURE 1. A, Kaplan–Meier curves showing adjusted survival for patients in the Chemo-RT and Surg groups. Survival difference is significant ($P = .000$). B, Kaplan–Meier survival curves for Chemo-RT and Surg subgroups: surgery alone (17), surgery and adjuvant external radiation therapy (19), and external radiation therapy followed by surgery (21). Survival differences are significant ($P = .0001$). *XRT,* External radiation therapy.

Chemo-RT group, 5 of the 8 patients with parietal pleural involvement alone underwent chest wall resection, and no patient in this group had a local recurrence.

Sixty-two of the 63 patients in the Surg group have died. One patient died after a pneumonectomy, and 1 patient died after lobectomy (operative mortality, 3.2%). Thirty-six patients died of cancer: second cancer in 2, cardiovascular disease in 6, pulmonary disease in 6, other causes in 5, and unknown causes in 7. Sites of recurrence for 23 of the 36 patients who died of cancer are shown in Table 4, according to the patients' original site of invasion and treatment group.

Twenty-five of the 47 patients in the Chemo-RT group have died. One patient died after a pneumonectomy (operative mortality, 2.1%). Nine patients died of lung cancer, 5 patients died of pulmonary disease, 2 patients died of a second cancer, 2 patients died of cardiovascular disease, 3 patients died of other causes, and 3 patients died of unknown causes. Sites of recurrence in the 9 patients who died of lung cancer are shown in Table 4.

Four patients who underwent resection after induction chemoradiotherapy had major complications. Aspiration developed in 1 patient, followed by pneumonia and acute respiratory distress syndrome, and the patient died. Acute respiratory distress syndrome developed in 2 patients, in association with pneumonia in 1 patient and bronchopleural fistula in 1 patient. One patient had a perioperative myocardial infarction.

DISCUSSION

In 1979, when our lung cancer database was constructed, tumors invading outside the lung were considered T3 and T3N0M0 lung cancers were classified as stage III.[7] In 1986, T3 and T4 descriptors distinguished tumors on the basis of their degree of invasiveness and associated clinical outcomes.[8] T3N0M0 tumors were now classified as stage IIIA, and T4N0M0 tumors were classified as stage IIIB. It was not until 1997 that T3N0M0 lung cancers were downstaged to stage IIB.[6]

TABLE 4. Recurrences by original sites of invasion

	Chemo-RT N = 9							Surg N = 23						
Site of metastases*	Parietal pleura	Chest wall	Mediastinal fat	Diaphragm	<2 cm carina	Pulmonary artery/atrium	No. of recurrences	Parietal pleura	Chest wall	Mediastinal fat	Diaphragm	<2-cm carina	Pulmonary artery/atrium	No. of recurrences
Lung	1	1	2	–	–	–	4	2	2	1	1	1	2	9
Chest wall	–	–	–	–	–	–	–	1	1	1	–	–	–	3
Mediastinum	–	–	–	–	–	–	–	–	–	1	–	–	1	2
Brain	1	–	–	1	1	1	4	3	4	–	–	–	–	7
Other distant sites	3	2	–	–	–	3	8	3	5	–	–	1	2	11

*Within the Chemo-RT group, sites of recurrence were noted in all 9 patients who died of cancer. In the Surg group, sites of recurrence were noted in only 23 of the 36 patients who died of cancer.

We have restricted this report to include only patients with invasive cancers as defined by the Fifth Edition of the American Joint Commission. Patients with satellite nodules are not included.

Our treatment of T3 and subsequently T4 NSCLC followed our approach for treating other patients with stage III disease. Before 1988, our treatment algorithm consisted of induction high-dose radiation therapy. With the advent of platinum-based chemotherapy, we began using induction chemoradiotherapy as the treatment of choice for all stage III lung cancers. Patients whose stage was determined only at surgery or on the basis of pathologic examination were treated in various ways, mostly by adjuvant radiation or surgery alone. These patients are now treated with adjuvant chemotherapy based on the results of the LACE meta-analysis.[9] Although T3N0M0 lung cancers were downstaged to stage IIB in 1997, we did not alter our treatment regimen for these tumors based on our positive results with induction chemoradiotherapy at that time.

The evolution of our treatment for T3 and T4 lung cancers, although based on our treatment protocol for patients with N2 disease, parallels the evolution of treatment for Pancoast tumors. Several series demonstrated superior results in terms of both resectability and outcome, with the introduction of induction radiotherapy before surgical resection.[10,11] More recently, the Southwest Oncology Group (9416, Intergroup trial 0160) has shown the superiority of neoadjuvant chemoradiotherapy in treating these patients, with a complete resection rate of 94% and 5-year survival of 54% for patients undergoing a complete resection.[12]

Unfortunately, our database does not discriminate between T3 tumors invading the chest wall and superior sulcus (although, in our experience, superior sulcus tumors represented a minority of patients in this report). It is recognized that these tumors respond to neoadjuvant treatment and may, at least theoretically, have a better prognosis than tumors invading the chest wall. However, our results for patients with both peripheral and central T3N0M0 and T4N0M0 NSCLC receiving neoadjuvant chemoradiation—with a median survival of 90 months, and 5- and 10-year survivals of 61% and 50%, respectively—argue for the superiority of aggressive neoadjuvant chemoradiation over any other treatment paradigm, demonstrating a greater than 2-fold survival difference. Although the subgroups of patients treated with neoadjuvant radiation, adjuvant radiation, and surgery alone were small, patients receiving neoadjuvant chemoradiation had significantly better results than these subgroups ($P = .0001$; Figure 1, *B*). Age was the only other independent variable affecting survival.

It is imperative that mediastinal nodes be evaluated with CT, PET, and in most cases mediastinoscopy, because neoadjuvant chemoradiotherapy regimens have also been effective in treating patients with stage IIIA-N2 lung cancer.[13,14] In the initial part of this series, invasive staging of the mediastinum was carried out only in patients with enlarged mediastinal lymph nodes, and complete lymph node dissections were performed only in patients with suspected nodal disease. As a result, only 41% of the Surg group had an invasive staging procedure, compared with 77% in the Chemo-RT group.

Given the relatively low negative predictive index for mediastinal staging by CT alone, especially for patients with a higher T stage, it seems highly likely that some patients in the Surg group were understaged. Most of them were treated before PET became available and mediastinoscopy was routine. Furthermore, 10% of those dying of their cancer had mediastinal recurrence (Table 4). On the other hand, despite a negative mediastinoscopy, some patients will have nodal disease; in those receiving neoadjuvant therapy, they also may remain understaged. Because the patients in this series were not randomized and staging was not uniform, the conclusions must be verified by a prospective study with standardized staging and resection criteria.

Perhaps the most significant problem with a study of this nature is the long time span over which it was conducted. Although the data were prospectively gathered, there have been significant advances in imaging and diagnosis. Surgical techniques have changed, as well as anesthetic and postoperative management. It is difficult to know how these factors may have affected the results: Most of the patients in the Surg group were treated earlier in the study, whereas most of the patients in the Chemo-RT group were treated only in the last 20 years. This may be important because on univariate analysis, decade of care was a significant predictor of mortality.

In this series, there was a disparity between the numbers of patients with parietal pleural involvement versus chest wall involvement in the Surg group versus the Chemo-RT group. In the Surg group, 30 of 56 patients (53%) with peripheral T3 tumors had only parietal pleural involvement, whereas 19 patients (34%) had chest wall involvement (Table 3). Although just 3 of the patients with parietal pleural involvement underwent a chest wall resection, local recurrence developed in only 1 patient. Adjuvant or neoadjuvant treatment may have contributed to this.

In the Chemo-RT group, only 8 of 38 patients (21%) with peripheral T3 tumors had parietal pleural involvement, and 5 of them underwent chest wall resection; 16 of the 38 patients (42%) had chest wall involvement. It is unlikely this disparity affected the results, because local recurrence is the principal issue of chest wall resection for patients with only parietal pleural involvement. On the other hand, the overall risk of local/regional recurrence was higher in the Surg group (14/63, 22%) than in the Chemo-RT group (4/47, 9%) (Table 4). This difference is likely even higher: Sites of recurrence were known for only 23 of the 36 patients who died of their cancer in the Surg group, whereas all sites were known for the 9 patients who died of their cancer in the

Chemo-RT group. This suggests that Chemo-RT affects local/regional recurrence and survival.

CONCLUSIONS

This analysis does have several biases that can be answered only in a prospective multicenter trial. Although only age and treatment group were independent predictors of mortality, variables such as age, FEV_1, and decade of care were significantly different between the 2 groups. During the course of this study, there was improvement in diagnosis, staging, and management. The resolution of CT scanners has changed, PET imaging is now available, and invasive staging of the mediastinal lymph nodes has become routine. As such, it is likely that a few of these patients were understaged or overstaged, affecting patient selection. All in all, however, the extended length of follow-up of patients in this series and the observed difference in survival (>2-fold) strongly support further evaluation of this aggressive approach.

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